## REMARKS

### 1. Preliminary Remarks

#### a. Status of the Claims

Claims 17, 20, and 29-32 are pending and under active consideration in this application.

### 2. Patentability Remarks

On pages 3-17 of the Office Action, the Examiner rejects claims 17, 20, and 29-32 under 35 U.S.C. §101 for lacking support in the specification for credible utility. The Applicant respectfully disagrees.

Specifically, the Applicant asserts that the Examiner has impermissibly applied a higher evidentiary standard for establishing utility of the claimed nucleic acids. The evidentiary standard that the Patent Office **should** use throughout *ex parte* examination in setting forth the utility rejection is preponderance of the totality of the evidence under consideration. A preponderance of the evidence exists when it suggests that it is more likely than not that the assertion is true. *See Herman v. Huddleston*, 459 U.S. 375 (1983). To overcome the presumption of truth of the Applicant's assertion of utility, the Examiner must establish by presenting countervailing facts that it is more likely than not that one of ordinary skill in the art would doubt (or question) the truth of the statement of utility.

The crux of the Examiner's rejection is that the Applicant's assertion that the claimed miR nucleic acids do bind and inhibit expression of LHFPL2 mRNA lacks credibility. The Examiner asserts that the prediction model taught by the Applicant provides no evidence that while the ability to predict hairpin-like structures and potential targets from genomic sequence in fact existed at the time of filing, validation of the true biological function of any predicted miRNA sequence requires analyzing miRNA patterns and testing the effects of miRNA expression in living cells (cited Krutzfeldt *et al., Nature Genetics* 38:514-519 (2006) on page 6 of the Office Action). Moreover, the Examiner further states that the experimental evidence provided in Dr. Chajut's Declaration (the "Declaration") fails to show that the claimed nucleic acids or for that matter SEQ ID NO: 354 is processed from a pre-miRNA complex (SEQ ID NO: 48) into a miRNA duplex necessary for interaction with the RISC complex and target inhibition (citing Cullen, *Nature Genetics* 37:1163-1165 (2005). The Examiner concludes that the claimed single-stranded sequences would not interact with the RISC complex and likely be degraded by nucleases. The Examiner states the only thing Applicant has shown is that hsa-miR-196b is present in the cell and can be knocked down.

A careful review of the basis of the rejection shows that the Examiner requires experimental certainty or 100% assurance that the claimed nucleic acids act or form a miRNA in order to remove any question of truth to the stated utility. Applicant submits this application of the law is impermissible.

Applicant submits that an assertion is credible unless (A) the logic underlying the assumption is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. For example, as discussed in §2107.02 III B of the MPEP, an assertion of utility would not be considered credible where a person of ordinary skill would consider the assertion to be "incredible in view of contemporary knowledge" and where nothing offered by the Applicant would counter what contemporary knowledge might otherwise suggest. Rejections under 35 U.S.C. §101 based on lack of credible utility have been sustained by federal courts when the applicant failed to disclose **any** utility for the invention or asserted a utility that could only be true if it **violated a scientific principle or was wholly inconsistent with contemporary knowledge in the art.** *See In re Gazave*, 379 F.2d 973 (CCPA 1967).

In response to the Examiner's assertions and the stated law above, the Applicant first asserts that the Examiner has provided no evidence to countervail that miRNA SEQ ID NO: 354 is likely to inhibit expression of the LHFPL2 protein. Whether or not the claimed polynucleotides actually exist in a biological system, and whether the true biological function of any predicted miRNA sequence has been validated according to Krutzfeldt (cited again by Examiner on page 6 of the Office Action) are irrelevant. The proper inquiry is instead whether a person of ordinary skill in the art would believe that the claimed polynucleotides **may be** used to modulate expression of the specific mRNA targets. Applicant submits evidence has been presented throughout the file history of this application.

The important consideration is that the Declaration clearly demonstrates that miR-hsa-196b (SEQ ID NO: 354) is capable of inhibiting LHFPL2 protein expression. Applicant further submits that the constructs and methods discussed in the Declaration were well known the art for testing a given sequence for RNAi activity.[1] Accordingly, unlike the facts in *Gazave*, the Declaration validates that Applicant's algorithm does not violate any scientific principles and is wholly consistent with contemporary knowledge regarding miRNA prediction algorithms.

With regard to the Examiner assertion that miR activity depends on dsRNA intermediates and the RISC complex that are not claimed, Applicant respectfully submits that the Examiner has simply identified derivative structures and processes that may be used once an active miR has been identified. In this application, Applicant has provided and claimed the key features that provide for regulation of LHFPL2. As a result, the claimed miR sequence (SEQ ID NO: 354) is a subcombination of the RISC complex of Cullen. A new product [or process] must be shown to be "operable"—that is, must be "capable of being used to effect the object proposed" in order to meet the utility requirement. *See*

[1] Meng *et al., Gastroenterology* 133:647-658 (2007) discusses the use of a reporter vector with altered 3'UTR of an exploratory target gene and antisense oligo to the target gene's endogenous miR sequence to validate the link between a miR and its target

*Mitchell v. Tilghman* 86 U.S. 287 (1873). This does not mean, however, "that a patented device [or composition] must accomplish all objectives stated in the specification. On the contrary, **subcombination** claiming is consistent with the utility requirement of §101 so long as what is described in the claim has utility in itself." *See Carl Zeiss Stiftung vs. Renishaw PLC*, 945 F.2d 1173 (Fed. Cir. 1991). Because Applicant shows the claimed miR inhibits LHFPL2 protein expression, the utility flows from this knowledge.

With respect to claims 20, 30, and 32, the Examiner asserts that there is no evidence verifying the expression of the hairpin SEQ ID NO: 48 comprising SEQ ID NO: 354 and its role in inhibiting a target gene and treating a disease (see Office Action pages 7 and 8). Applicant again asserts that it is the Examiner, not the Applicant, that must provide by a preponderance of the evidence that Applicant's asserted utility fails and that the expression of hsa-miR-196b is not due to the hairpin precursor as set forth in SEQ ID NO: 48. As discussed in Applicant's response of December 1, 2008, paragraphs 0199 and 0203 of the specification and Figure 22 show that has-miR-196b (GAM7553, which is related to SEQ ID NOS: 354 and 48) was specifically detected in a HeLa cell cDNA library. In response, the Examiner has failed to provide any evidence whatsoever to doubt that the claimed hairpin precursor would be processed to yield a miR capable of regulating LHFPL2 protein expression. In summary, Applicant asserts that credibly utility of the claimed nucleic acids exists after consideration of the teachings of the specification in combination with Examiner's failure to provide greater than 50% assurance that one of ordinary skill in the art would doubt (or question) the truth of the statement of utility as well as the Applicant's unnecessary step of providing the Examiner with validation results described in the Declaration.

With regard to the Examiner's rejection regarding specific and substantial utility, the Examiner asserts that Applicant has not demonstrated that modulation of LHFPL2 would in fact modulate LHFPL, LHFPL3, or LHFPL4 as well as the specific outcome of such interaction. Applicant reasserts that the claimed nucleic acids are of a specific and unique nature because these nucleic acids regulate the translation of mRNAs from the specific target gene LHFPL2. Applicant also presents again the fact that study of the regulation of LHFPL2 is a public benefit one reason which is the ability of the claimed nucleic acids to modulate the expression of the LHFPL2, the human homolog of hscy (gene symbol TMHS) and an orthologous gene known to be related to hearing, the human homolog of LHFPL (*see also* abstract of Shabbir *et al., J. of Medical Genetics* 43:634-640 (2006)), an orthologous gene known to be translocated in chromosomal aberrations in lipomas. Accordingly, Applicant asserts that the claimed nucleic acids have specific, substantial and credible utility. In view of the foregoing, Applicant requests that the rejection of claims 17, 20, and 29-32 under 35 U.S.C. §101 for lacking utility has been overcome and therefore should be withdrawn.

**a. 35 U.S.C. §112, First Paragraph (Enablement)**

On page 8 of the Office Action, the Examiner maintained the rejection of claims 17, 20, and 29-32 under 35 U.S.C. §112, first paragraph for allegedly failing to comply with the enablement requirement. The Examiner asserts that since the claimed invention is not supported by a credible asserted utility, one skilled in the art would not know how to use the claimed invention. Applicant respectfully disagrees.

As discussed above, the claimed nucleic acids have a credible, substantial and specific utility, namely in modulating expression of the LHFPL2 transcript, which in turn, may respectfully modulate LHFPL, an orthologous gene known to be translocated in chromosomal aberrations in lipomas. Therefore, the Applicant submits that the function of the claimed nucleic acids was known at the time of filing. In view of the foregoing remarks Applicant respectfully requests that the rejection of claims 17, 20, and 29-32 under 35 U.S.C. §112 for lack of enablement has been overcome and therefore should be withdrawn.

**3. Conclusion**

Applicant respectfully submits that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examine is encouraged to call the undersigned at the numbers listed below.

Respectfully submitted,

POLSINELLI SHUGHART PC

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